Toward Real-Time Modeling of Human Heart Ventricles at Cellular Resolution: Simulation of Drug-Induced Arrhythmias

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***Abstract*—We have developed a highly efficient and scalable cardiac electrophysiology simulation capability that supports groundbreaking resolution and detail to elucidate the mechanisms of sudden cardiac death from arrhythmia. We can simulate thousands of heartbeats at a resolution of 0.1 mm, comparable to the size of cardiac cells, thereby enabling scientific inquiry not previously possible. Based on scaling results from the partially deployed Sequoia IBM Blue Gene/Q machine at Lawrence Livermore National Laboratory and planned optimizations, we estimate that by SC12 we will simulate 8–10 heartbeats per minute — a time-to-solution 400–500 times faster than the state-of-the-art. Performance between 8 and 11 PFlop/s on the full 1,572,864 cores is anticipated, representing 40–55 percent of peak. The power of the model is demonstrated by illuminating the subtle arrhythmogenic mechanisms of anti-arrhythmic drugs that paradoxically increase arrhythmias in some patient populations.**

I. Introduction

Sudden cardiac death (SCD) from cardiac arrest is the most common cause of death worldwide, accounting for over 50 percent of all deaths from cardiovascular disease and 250,000 to 300,000 deaths annually in the United States [1]. While much controversy exists, SCD is generally accepted to result from arrhythmias, predominately ventricular fibrillation, and hence can be considered an electrical dysfunction of the heart. During a normal heartbeat, Purkinje fibers, a specialized impulse conduction system, trigger the heart ventricles to contract in a uniform and orderly fashion. Each triggering event produces activation (termed *depolarization*) of the ventricular heart cells, followed by a recovery (termed *repolarization*) with a delay of approximately 300–500 ms. In contrast, an arrhythmia is thought to arise from a re-entrant activation that follows an abnormal circular path and produces a continuous and self-regenerating cycle of activation.

Despite more than 50 years of intense research, the underlying mechanisms of arrhythmogenesis remain elusive. Current experimental techniques cannot resolve initiation events at the cellular level, and *in situ* measurements in a beating heart will remain a challenge in the foreseeable future. For this reason, we believe that detailed cardiac simulations have the greatest potential to illuminate the details of the formation and persistence of re-entrant activation patterns. Understanding gained from high fidelity simulations will help to better apply existing therapies and spur the development of new therapies with greater efficacy and fewer deleterious effects.

Detailed cardiac models include biophysically accurate representation of cells, the assembly of cells into anatomically accurate organ-level structures, and models of the cell-to-cell electrical coupling including preferred electrical conduction along the complex muscle fiber structure of the heart. Previous cardiac simulation implementations are limited in biophysical detail of the cellular models, size of the model structure (e.g., rabbit vs. human heart), spatial resolution, and practical length of simulation time. Published studies typically cite spatial resolutions of 0.2–0.3 mm and 20–32 million active elements [2]–[5] and simulation times of up to tens of heartbeats.

To address these limitations, we have developed *Cardioid*, a high-performance cardiac simulation tool with detailed cell representations and support for heart geometries with near-cellular spatial resolution based on full-size human ventricle anatomy [6]. We plan to use *Cardioid* to simulate the application of an anti-arrhythmic drug that is known to increase arrhythmias in some patients [7]. This study, which includes application and clearance of the drug and the sporadic arrhythmia events that occur in certain circumstances [8], requires both 0.1 mm resolution and simulation of 5,000 heartbeats or more, a task beyond the capability of other codes.

To meet the extraordinary computational demands of such a study, *Cardioid* has been highly optimized for execution on the *Sequoia* IBM Blue Gene®/Q (BG/Q) machine at Lawrence Livermore National Laboratory (LLNL). We predict a factor of 400–500 throughput improvement over previous methods (see [9], [3] and [10]) projected to our planned simulations. Through use of low-level communication protocols, we attain near-perfect weak scaling. With judicious use of cache and

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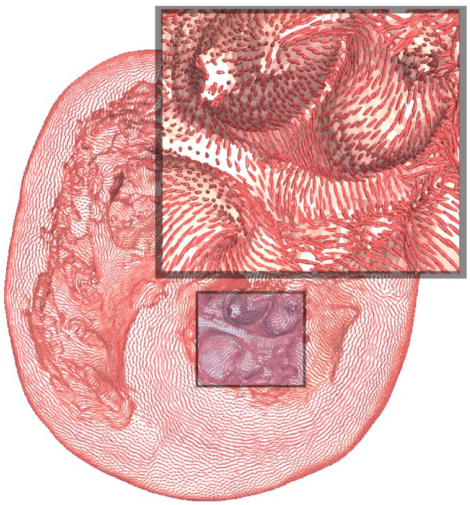

Fig. 1. Top view of ventricles looking down on the chambers. The inset shows details of the fine structures of the endocardium surface, including papillary muscles. The illustrated cardiac cells that are in red (not to scale) show the fiber direction.

registers, minimization of memory accesses, utilization of hardware threading, hardware assisted barriers for intranode synchronization, and exploitation of the SIMD instruction set, we are able to attain 43% of peak performance per computational node despite having only 1600 floating point operations per grid cell per iteration. This translates to over 4.3 Pflop/s on half the machine (already demonstrated) and over 8.6 Pflop/s projected on the full 1,572,864 core system (based on the demonstrated near-perfect weak scaling). This represents a speedup of a factor of 50 with respect to the unoptimized code. With further optimization we hope to exceed 10 Pflop/s on the full Sequoia.

II. Computational Model

The electrophysiology of human heart ventricles is simulated as the ensemble behavior of individual cells that are physically and electrically connected (see Figure 1). Cells become electrically active as a result of charged ionic species traversing each cell's membrane through specialized protein structures called ionic channels. On every heartbeat, each cell activates and deactivates with a spike in the cell membrane electrical potential called an action potential (AP, see Figure 6). The AP's are transmitted from cell to cell via specialized gap junctions that pass ionic currents, and the cells are arranged into fibers with increased conduction in the axial direction.

Two approaches to modeling the time evolution of the AP are in wide use. The first, more accurate method, is the bidomain model where the intra- and extra-cellular regions of the heart are modeled by coupled non-linear reaction-diffusion equations. The second method, called the monodomian model, is a simplification of the bidomain model using the assumption that the conductivities in the intra- and extra-cellular regions are proportional to each other. We employ the monodomain approximation which is very commonly used in the field because the results are sufficiently accurate without the additional cost of the bidomain method [11].

In the monodomain model the time evolution of the electrical potential of the cell membrane (V_m) is given by

$$C_m \frac{\partial V_m}{\partial t} = \frac{1}{\beta} \nabla \cdot (D \nabla (V_m)) - I_{\text{ion}} + I_{\text{stim}} \qquad (1)$$

with a zero-flux condition imposed at the heart tissue boundary. C_m is the membrane capacitance, β is the surface to volume ratio, and I_{stim} is the external stimulus current. The conductivity D is a spatially varying anisotropic tensor and is determined by the fiber structure of the heart. I_{ion} is the sum of all ion currents, and a variety of models for these currents have been proposed. Such models are called tissue models or reaction models and define the state of a heart cell in terms of values of ionic species concentrations and gate variables, where a gate expresses the probability that a particular ion channel is open. The evolution of the state variables (concentrations and gates) is expressed as a set of coupled nonlinear ODE's. The ionic currents for a given cell are independent of those of the other cells. The coupling between cells arises through the diffusion term of equation (1).

In 2006 ten Tusscher, et al. [12] developed a reaction model (hereafter referred to as TT06) in which the state of a cell is defined by 5 ion concentrations and 13 gates. The TT06 model simulates three types of cells: epicardial (epi), M and endocardial (endo) cells. Epi and endo cells are located respectively near the outside and inside walls of the heart. M cells, generally thought to be located in the mid-myocardium, are characterized by their unique repolarization properties. We have modified the TT06 model to add a late sodium current with an associated gate to better reproduce the observed variation of action potential duration (APD) in various cell types (see section VI). We refer to this enhanced model as TT06e.

The ODE's in TT06e can be divided into two classes. The time derivative for 12 of the 14 gate variables can be expressed simply as

$$\frac{dg_\beta}{dt} = (\mu_\beta(V_m) - g_\beta)(\tau_\beta(V_m))^{-1} \qquad (2)$$

Notice that the evolution of each gate depends only on the value of the gate variable g_β and the membrane voltage, V_m. This observation is exploited in the optimization and discussed in section IV. The time derivative of the remaining degrees of freedom g^*_α (2 gates and 6 ion concentrations) is expressed in the general form

$$\frac{dg^*_\alpha}{dt} = F(\{g^*_\alpha\}, \{g_\beta\})$$

where F is a nonlinear function. For simplicity we refer to the first set of equations as gate equations and the remainder as non-gates.

We define a 3D Cartesian grid in which each cell either contains heart muscle tissue or does not. Our computational domain is defined as the union of all the tissue cells.

We discretize the diffusion term using a finite-volume approach, in which we replace the divergence operator with a surface integral over the six faces of each cell. Since the conductivity tensor D is a general anisotropic tensor, calculating the flux through each cell surface requires the evaluation of all three components of ∇V_m. The gradient is calculated using a simple finite difference algorithm on the values of V_m in the cells nearest to the surface considered. Setting the flux to zero through grid cell surfaces located at the boundary of the computational domain enforces the boundary conditions. If some neighbor cells required for the stencil are outside the computational domain, the finite difference scheme is locally modified to use only available values of V_m inside the computational domain. This results in a 19-point stencil operator with weights dependent upon cell location. In practice, the weights are precomputed at the beginning of a run and stored for each cell. The time-integration is accomplished with a forward Euler scheme except for the so-called m-gate. For this gate τ (equation (2)) can become quite small and an exponential integration suggested by Rush and Larsen [13] allows a much larger time step than forward Euler.

Our parallelization strategy consists of a hybrid approach where we make use of message passing and threading. We first decompose the heart into domains of tissue cells. Domains are constructed to minimize the time to solution and are assigned to compute nodes in a one-to-one fashion. Due to the high overhead of MPI, message passing in performance critical code sections is performed using lower-level primitives (see section IV-B). The threading strategy is described in detail in section IV-C.

Because of the complicated heart geometry and the fact that the domain workload depends on the domain size and shape as well as the number of tissue cells it contains, constructing domains with perfect load balance is prohibitively difficult, so we do not attempt to equalize the load over all domains. Instead, we minimize time-to-solution by ensuring that no domain exceeds a fixed maximum load, typically a few percent higher than a hypothetical perfectly balanced case. The result is not a balanced load in the usual sense, as some domains may have a workload that is much lower than average. However, the number of such domains is generally quite small and the impact on overall efficiency is negligible.

Brick-shaped trial domains are generated using various strategies depending on the simulation size and geometry (whole heart or wedge) and number of available nodes. The load for each trial domain is estimated using a performance model, and the trial set is modified until all domains satisfy specified load requirements. Domains are not required to have the same size, shape or number of tissue cells for each node, and the number of threads assigned to diffusion or reaction is allowed to vary across nodes based on performance model predictions. We also allow use of different kernels on different nodes since kernel performance can vary greatly (see section IV-E) depending on the details of the domain size and shape as well as number of cells in the domain.

This approach is both flexible and robust over a wide range of highly anisotropic heart geometries (3 million to 370 million cells) and node counts (128 to 96k). For cell and node counts at the larger end of this spectrum, trial domain strategies with additional constraints can be used to produce domains with characteristics that are well tuned to details of the computational kernels such as L1 cache usage and SIMD vectorization traits. Based on trials described in section V, we estimate a time-to-solution for a 370 million cell heart running on the full Sequoia machine will be less than 110% of the time for a corresponding ideal block.

III. Target Architecture

Sequoia, located at Lawrence Livermore National Laboratory, is the first and largest installation of the BG/Q architecture. When fully operational, it will employ 98304 nodes and nearly 1.6 million processor cores to achieve a peak performance of roughly 20 PFlop/s. On a per-node basis, BG/Q will out-perform its predecessors Blue Gene/L and Blue Gene/P by a factor of 36 and 15, respectively.

Each BG/Q node is based on a system-on-a-chip processor fabricated with 45 nm technology [14]. By integrating processors, memory subsystem, and chip-to-chip communication subsystems on a single chip, the compute node achieves both outstanding power efficiency and reliability. Reliability is further enhanced by deploying state-of-the-art soft-error mitigation and error correction techniques throughout the design. Functionally, the chip contains 16 compute cores and 1 supplemental core to handle operating system tasks. Each core supports four-way simultaneous multithreading (SMT) and two-way concurrent instruction issue: one integer, branch, or load/store instruction and one floating-point instruction per clock cycle. Within a thread, dispatch, execution, and completion are in order. Four threads per core are sufficient to fully utilize the execution pipelines, prevent memory latency from adversely affecting performance, and avoid the necessity of out-of-order execution. Each core contains a quad SIMD double precision floating point unit (FPU) capable of 8 floating point operations (fused multiply add) per cycle. The 16 user processor cores at 1.6 GHz gives a BG/Q node a peak performance of 204.8 GFlop/s. Each processor core has a 16+16 kByte L1 instruction and data cache with a sophisticated pre-fetch. The processors share a central 32 MByte L2 cache with 563 GByte/s bisection bandwidth. The node main memory is 16 GByte of directly attached SDRAM-DDR3 providing 42.7GB/s total bandwidth.

The BG/Q L2 cache provides hardware support for transactional memory and speculative execution. These techniques facilitate execution of threaded code with potential data conflicts and dependencies, by allowing threads to run speculatively in parallel, while detecting and managing conflicts and dependencies as they occur. The L2 cache also supports atomic operations, which we use for thread synchronization. For operations such as locking and barriers, and for work-queue management, these atomic operations have much less latency than software implementations that use the traditional load-linked/store conditional or compare-and-swap mechanisms,

especially for a large number of threads. Haring, et al. [14] gives an example of a 30x reduction in latency for 64 threads to obtain a ticket lock (where each thread obtains a unique number) using the atomic LoadIncrement instruction.

An integrated five-dimensional torus serves as the principal node-to-node communication network and also handles collectives and fast interrupts. Compared to the 3D torus architecture of its predecessor machines, the 5D torus in BG/Q markedly decreases the number of hops required to reach the farthest node in the machine from any given node, and thereby both increases the bandwidth and reduces the latency of node-to-node communication. The 5-D nearest neighbor exchange bandwidth is roughly 1.75 GByte/s per link with a latency of 700 ns. BG/Q is water cooled and has achieved a power efficiency of over 2 GFlop/s/Watt on a Linpack benchmark.

The Sequoia installation has one I/O node for every 128 compute nodes, theoretically supporting up to 4 Gbyte/s bandwidth per I/O node to a file system.

IV. Optimization strategy

In designing an optimization strategy, a number of significant challenges must be addressed. Chief among these is the relatively small amount of available work per core. Our discretization of a typical human heart with a grid resolution of 0.1 mm has about 370 million grid cells of heart tissue. On Sequoia this amounts to about 3800 cells per node, or fewer than 250 per core. In this aggressive strong scaling regime, merely tuning C/C++ code to the BG/Q architecture is not enough. It is also necessary to modify the computational model to eliminate high-cost operations and expose concurrency while always maintaining fidelity to the underlying biology. Only this combination of hardware-aware and biology-aware tuning can achieve the best possible time-to-solution.

A. Biology-aware tuning

In TT06e there are 32 computationally expensive functions to be evaluated for each grid cell at each time step. These functions share the common form

$$f(V_m) = \frac{\sum_{i=0}^{N} A_i \exp(B_i V_m)}{\sum_{j=0}^{M} C_j \exp(D_j V_m)} \tag{3}$$

For example, μ and τ (see equation (2)) for the fGate are given by

$$\mu = \left(1 + \exp\left(\tfrac{V_m+20}{7}\right)\right)^{-1}$$

and

$$\frac{1}{\tau} = \frac{1.0 + \exp\left(\frac{25.0-V_m}{10.0}\right) + 80.0/\left(1.0 + \exp\left(\frac{V_m+30.0}{10.0}\right)\right)}{562.0\exp\left(\frac{-(V_m+27.0)^2}{240.0}\right) + 31.0}$$

The majority of the computational effort in updating the state variables is associated with evaluation of these functions, so it is essential to find efficient ways to compute them.

The form and parameters in equation (3) are obtained not from any biological "first-principles", but are rather chosen to give reasonable limiting behavior and to fit experimental data which are subject to measurement error. Suppose form (3) is replaced with a lower-cost form such as a rational function approximate

$$f(V_m) \approx f_a(V_m) = \frac{\sum_{i=0}^{m} a_i V_m^i}{1 + \sum_{j=1}^{\ell} b_j V_m^j}$$

Such a replacement is justifiable as long as the limiting behavior is respected and the fit to data is equally good. We can in fact replace all 32 functions with rational functions having coefficients chosen to minimize the cost of evaluation while maintaining a relative error of $\epsilon = 10^{-4}$, where

$$\epsilon = \frac{\max_{V_m \in I} |f_a(V_m) - f(V_m)|}{\max_{V_m \in I} f(V_m) - \min_{V_m \in I} f(V_m)},\ I = [-100, 50]\ \text{mV}.$$

Approximates for each of the 1D functions are constructed separately, so the various rational function approximates contain polynomials of different order ranging from 1–18 in the numerator and 1–11 in the denominator.

One additional modification to the TT06e formulation is very useful. The rate of change of the potassium concentration K_i depends not only on the membrane potential, V_m, and other reaction state variables, S, but also on the rate of change of V_m due to the external stimulus, I_{stim} and diffusion, dV_m^D/dt:

$$\frac{dK_i}{dt} = -C[I_p(V_m(t), S(t)) + \frac{dV_m^D(t)}{dt} + I_{\text{stim}}(t)] \tag{4}$$

This introduces a coupling between the diffusion and reaction calculations. However by adding and subtracting the rate of change of the voltage due to reaction, dV_m^R/dt, equation (4) can be rewritten as;

$$\begin{aligned}\frac{dK_i}{dt} &= -C\left(Ip - \frac{dV_m^R(t)}{dt} + \frac{dV_m^R(t)}{dt} + \frac{dV_m^D(t)}{dt} + I_{\text{stim}}(t)\right)\\ &= -C\left(Ip - \frac{dV_m^R}{dt} + \frac{dV_m}{dt}\right)\end{aligned}$$

Rearranging terms and introducing the change of variable $V_m^K = K_i/C + V_m$ produces

$$\frac{dV_m^K}{dt} = -\left(Ip - \frac{dV_m^R}{dt}\right) = f(V_m(t), S(t))$$

and in terms of the new variable the coupling is removed.

B. Internode communication

With TT06e expressed in terms of rational function approximates, about 1600 floating point operations per grid cell are required to evaluate equation (1). Assuming 50% of peak performance and 3800 cells/node, this executes within 70 μs of wall clock time. As this is practically all of the computation in a time step, communication and synchronization operations must be optimized to be fast compared to 70 μs.

Internode communication is driven by the diffusion operator, which requires a halo exchange of ghost cells to satisfy the finite difference stencil. As we are well into the strong scaling regime, the surface to volume ratio is high (about 40–50%) and the message sizes are small. We implemented the halo exchange using MPI Isend and Irecv and found unacceptably high latencies of about 300 μs per time step. This forced us to

abandon MPI calls and reimplement the halo exchange using the BG/Q low-level Systems Programming Interface (SPI).

Our optimized halo exchange is based on a remote-put strategy and takes advantage of the fact that communication descriptors whose specification includes message size, destination and routing can be constructed at initialization and associated with a first-in, first-out queue (FIFO) that is used for the remainder of the simulation. Communication is initiated by copying data from its regular storage location to the FIFO memory area and adjusting the tail pointer of the FIFO. This triggers the message engine to copy data to the network using the DMA instead of CPU resources. Message delivery completion is checked by monitoring counters for each message. On each node two receive buffers are used in alternation to avoid a race condition that could overwrite received data.

Large scale benchmarks on up to 48k nodes demonstrate that the SPI based halo exchange is completed in approximately 15 μs, a 20-fold improvement in communication time. Moreover, the CPUs are completely free during practically all of this time, allowing full opportunity to overlap computation. Other less frequent communication, such as initialization tasks and data aggregation for I/O, is performed with MPI.

C. Threading model

Initially we had planned to exploit the concurrency of multiple cores per node as well as multiple threads per core by decorating key loops with OpenMP pragmas. Unfortunately this also proved to be a source of unacceptable latency. On BG/Q the fork/join overhead for a single parallel *for* loop with 64 threads is nearly 15 μs. Hence, we are forced to abandon the model of using OMP pragmas to manage threads within our main time step loop. Instead, we begin a parallel section before the time step loop and manage the threads explicitly.

Our overall threading strategy is shown in Figure 2. The modifications to the potassium current described in Section IV-A allow us to run reaction and diffusion concurrently. Of the 16 cores on the node, we designate a number of cores to be responsible for diffusion and the halo exchange. The remaining cores are responsible for the reaction model, time-integration loop, and most data copying/reformatting operations. The assignment of cores to diffusion or reaction can be specified independently for each node and is configurable at run-time. For subdomains containing virtually all tissue we typically assign two cores to diffusion; depending on the load-balancing strategy, subdomains that are largely non-tissue will have fewer cores assigned to reaction. Synchronization between the diffusion and reaction threads and barriers within groups of threads are handled using the fast L2 atomic operations provided by the hardware, reducing associated overhead to under 1 μs.

There are several advantages to assigning threads in this manner. A principal consideration is that each core has its own L1 cache that is shared among the hardware threads. Assigning diffusion and reaction to separate cores simplifies cache management and allows us to balance the difference

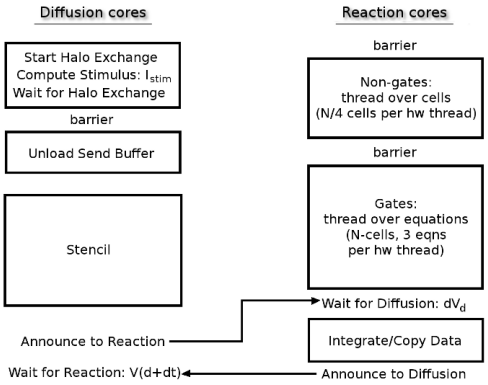

Fig. 2. Threading strategy. The diffusion and communication are shown on the left, and the reaction term on the right.

in computational intensity between diffusion and reaction by adjusting the number of cores assigned to the respective pieces. Additionally, SPI communication costs are covered by computation on most of the cores. Finally, since L2 bandwidth is on a per-core basis, copy operations are performed on the group with the larger number of cores.

D. Reaction calculation

The low level optimization of the reaction calculation is guided by the features of the BG/Q memory system and compute cores. Because of limited memory bandwidth (32 bytes/cycle/core from L1 and approximately 8 bytes/cycle/core from L2), data reuse is critical to prevent starvation of the quad SIMD FPU, which requires 96 input operand bytes/cycle for a quad fused multiply add (FMA). Such unfavorable bandwidth to Flop/s ratios are a typical feature of modern architectures. It is of course equally critical to "SIMDize" the calculation to exploit the vectorization potential of the SIMD instruction set. We chose the rational function approximates introduced in section IV-A specifically to address these two challenges. Polynomial coefficients can be kept in registers for reuse over many evaluations, and SIMDization is facilitated by the fact that the same polynomial is evaluated for all grid cells. To avoid the complexities of inline assembly, vector intrinsics (or "built-ins") are used to generate SIMD instructions.

There is no coupling between the 12 gate functions, so each has its own separate data stream. Assigning 3 gate functions to each of the 4 hardware threads on a core allows us to store different polynomial coefficients in registers for each thread. This is valuable since each of the four hardware threads per core has its own register bank, corresponding to 4k/core of storage in registers (compared to 16k in L1 cache). The varying polynomial degrees in the rational function approximates complicates the instruction balance within a single thread and impacts load balance, but this is largely remedied by loop skewing and the fact that only two of four threads are required to fully utilize the dual-issue instruction capability; the instruction units can remain heavily utilized even if one or

two threads finish early. We found that performance was highly sensitive to loop unrolling, and judicious use of unrolling had to be enforced. Greater unrolling causes register spilling, the cost of which is exacerbated by the write-through L1 cache. Register pressure is reduced by storing four different coefficients per register (instead of four copies of the same coefficient) and replicating ("splatting") into operand registers when needed. This technique can also favorably shift the mix of floating point and integer instructions. Finally, we had to bear in mind that our goal was more complicated than obtaining the fastest single gate function, but the fastest computation of all 12 gates. Thus, some routines had to be restricted (e.g., in terms of register-to-register moves or loop unrolling) so that other routines, sharing limited resources, could run more effectively.

Optimization of the non-gate functions is more challenging because of a much greater diversity in the mathematical forms of the equations and because all 20 state variables are needed in the evaluations. With no obviously beneficial way to assign equations to hardware threads, work is instead partitioned by dividing the grid cells on each core among the threads. This has the unfortunate side effect of limiting the ability to use the per-thread register banks to store the large number of coefficients, as each thread evaluates the same functions. Deep loop unrolling was of limited utility because extreme register pressure when unrolling could result in a catastrophic number of register spills. This was largely ameliorated through an application of the aforementioned technique of splatting coefficients from a table held in registers to operand registers. When employing intrinsics, this work is more painstaking than in the analogous case with assembly, as it is the register coloring and scheduling of the compiler that dictates when this method proves beneficial or pernicious. The third and final hurdle we faced involved the calculation of the log functions. We tailored the polynomial expressions needed to compute our log functions for the known, physically-relevant range of values that we might encounter and exploited SIMD instructions to great advantage.

E. Diffusion calculation

Mathematically, the diffusion calculation is simple. It is only a sum over the 19 stencil points of voltages multiplied by pre-computed coefficients. Due to fiber orientation, these coefficients are different for each grid cell and cannot be reused. The ratio of memory access to arithmetic is thus unfavorably high. Nevertheless, performance does improve with SIMDization obtained by loading the voltages of four adjacent (in memory) grid cells into registers and performing the stencil arithmetic for all four at once. Careful use of register swaps and shifts reduces the number of load operations that are needed. Further reduction in load bandwidth is achieved by representing the diffusion coefficients in single precision. This is reasonable because the fiber direction and conductivity tensor are not known to high precision.

One drawback of our diffusion kernels is that the grid cells assigned to a node must be represented in memory as a rectangular block. This allows the use of fixed memory offsets to locate stencil points, but requires a copy operation at each time step since reaction performance is optimized by a different memory layout. The fact that not all memory locations in the block correspond to tissue cells creates an additional inefficiency since some SIMD vectors will contain non-tissue cells. For domains with a large number of non-tissues cells, such as those near the heart boundary, the inefficiency of calcuating non-tissue cells outweighs the SIMDization advantage so we switch to an alternate non-SIMD kernel.

F. Validation

The optimized code has been carefully validated to ensure biological fidelity. Tests of a single cell paced (stimulated) at various prescribed intervals agree very well with published results [12]. We also compare to a TT06 benchmark suite presented in Niederer, et al. [15] involving eleven different electrophysiology codes that use a variety of numerical techniques and computational grids. We find excellent agreement between *Cardioid* and other finite difference codes. The fully anisotropic conductivity tensor was tested using the Method of Manufactured Solutions for a steady state solution of Eq. (1). As expected, the finite volume discretization error is $O(h^2)$ compared with the analytic solution for a grid spacing h.

V. Performance and Scalability

A. Timers and floating point performance counters

BG/Q provides a low-overhead CPU time base register which can be used to implement low cost *in situ* timers for monitoring time spent in different parts of the code. This register, which counts clock cycles, can be accessed via the inline call GetTimeBase() in only 1 cycle.

Each BG/Q core provides 24 counters that can monitor a variety of core events including counting floating point operations. Converting counts to Flop/s requires multiplication by appropriate weights: 1 for addition, subtraction, multiplication, and other non-storage operations, 2 for fused multiply-add, and 8 for division and square root. The corresponding SIMD instructions have four times the weight, i.e., 8 for a quad FMA. Using the IBM Hardware Performance Monitoring (HPM) library, operation counts are summed across all the cores on all nodes and divided by the elapsed time to get the throughput in PFlop/s. Measured HPM throughout values have been verified by directly counting operations using a small test system.

B. Performance and scaling

To demonstrate the effectiveness of our optimizations, we have compared the optimized *Cardioid* with an unoptimized version based on reaction code fom the CellML model repository and a simplistic implementation of the diffusion operator. The optimized code exhibits much better weak scaling than the unoptimized version (which uses MPI and OpenMP). On average, the optimized code executes about 50 times faster than the unoptimized code.

In order to estimate full machine performance for a human heart simulation at 0.1 mm resolution, we have performed

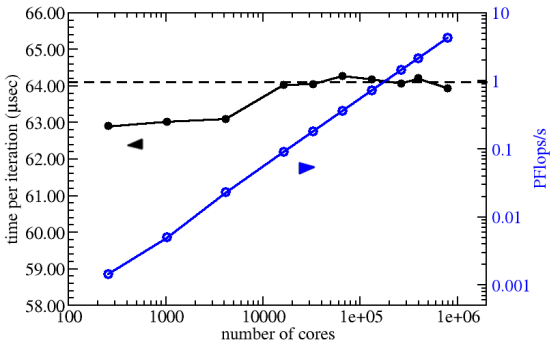

Fig. 3. Weak scaling of uniform block of heart tissue using optimized *Cardioid* code on BG/Q. The time per iteration (in μs) is shown in black, and the throughput (in PFlop/s) is shown in blue.

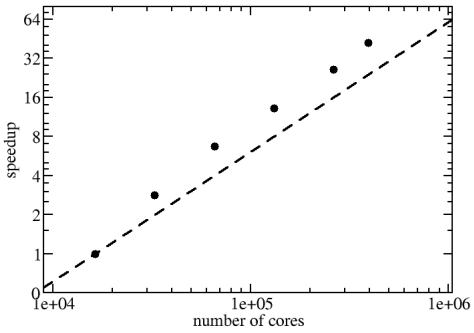

Fig. 4. Parallel speedup of 370 million cell heart, normalized against the 16,384 core case. The dashed line represents perfect scaling.

weak scaling tests on a tissue block having 3584 grid cells per node. The results are shown in Figure 3. We observe excellent weak scaling from 16,384 cores all the way up to 786,432 cores, one half of the full machine, with the time per iteration remaining constant and the measured floating point performance increasing linearly with the number of cores. This confirms that communication costs do not grow with increasing problem size, and that the code is capable of operating efficiently at very large task counts. It is therefore not unreasonable to extrapolate these curves another factor of two to the full machine and expect excellent parallel efficiency at full scale. On the half-machine our throughput exceeds 4.3 PFlop/s, which is over 43% of peak. Combined with our perfect weak scaling, we should exceed 8.6 PFlop/s on the full Sequoia once it is available.

Figure 4 shows the strong scaling performance for human heart simulations with 370 million tissue cells using up to 393,216 cores (one quarter of the full machine). The curve reflects two competing effects. The relatively poor throughput at 16,384 cores is due to coarse-graining in the domain decomposition, resulting in a large number of non-tissue cells per domain and correspondingly poor efficiency in the diffusion calculation. As the core count increases, performance improves as increased flexiblity in domain formation enables more efficient utilization of the hardware vector units. However, performance decreases as the number of cells per core shrinks since there is less work available to cover overhead. At 393,216 cores such overhead costs are still relatively small, but as the core count increases further, we expect a drop-off in scaling, as the number of grid cells per node will dip below 4000 at full machine (as compared to over 350,000 at 16,384 cores). While *Cardioid* is highly optimized for small cell counts (as shown by the floating point performance in Figure 3), the operating margins at such light workloads are so narrow that normally inconsequential overhad costs such as loop startup and function calls become significant. If we were merely interested in achieving high flop rates, it would be easy to construct systems with larger local data sizes. Simulations with a large number of cells per core have been measured at over 54% of peak. However, our goal is to optimize the time to solution of a real scientific application, thus necessitating the far more difficult task of optimizing performance at the far end of the strong scaling curve.

Because of the additional geometric complexity of the heart compared to a simple block of cells, another key indicator of our ability to obtain high performance at full scale is the ability of the domain decomposition algorithm to produce domains that minimize efficiency losses. Although we have not had access to 96k nodes for full scale tests, we have verified that the domains we would use at 96k nodes perform as expected in small scale tests. In particular, we have run single node test cases for domains that represent the full spectrum of brick size/shape and number of cells that are present in a 96k decomposition and verified that all satisfy the maximum load criteria. We have also simulated a geometry consisting of 8k domains selected from the 96k decomposition. This test not only verified that all domains performed within allowable limits, but that throughput was not slowed by communication times for non-ideal domains.

Finally, in addition to the performance trials just described, we have confirmed the stability of the code with a 40 heartbeat run using a 370 million grid cell heart geometry on 8,192 BG/Q nodes.

With continued algorithmic improvements and additional refinements to our optimization strategy, we expect to obtain performance on heart geometries that is nearly comparable to that of a homgeneous tissue block. We expect to achieve our target throughput of 8–10 heartbeats per minute on our 370 million grid cell heart on the full system and obtain flop rates approaching 50% of peak.

C. Time-to-solution

We compare the *Cardioid* time to solution with those of other leading cardiac electrophysiological models. We were able to identify three such efforts, all having published or presented in 2011, namely [9], [3] and [10]. All three invoke the monodomain approximation and utilize a reaction-diffusion model based on either [12] or [16]. All utilize an explicit time integrator for the reaction phase, and two of the three

TABLE I
THROUGHPUT (HEARTBEATS PER WALL CLOCK MINUTE) OF CARDIAC ELECTROPHYSIOLOGY MODELS TARGETED TO HPC SYSTEMS.

Author	Resolution	Grid cells	Raw thrpt	Norm. thrpt
Pope	0.2mm	32.5M	0.027	0.0024
Niederer	0.25mm	26M	0.025	0.018
Krause	0.0625mm	1560M	0.0015	0.0065
Mirin	0.1mm	370M	9.0 (est.)	9.0 (est.)

offer an implicit option for the diffusion phase. The quoted performance figures pertain to different sized hearts and are largely exclusive of I/O. Results are shown in Table I.

The raw throughput is defined as the number of simulated heartbeats per wall minute. In order to compare codes, we linearly scale raw throughput to 370M, the number of tissue grid cells for the study herein, to get normalized throughput, which appears in the rightmost column of the table. We believe that the published time steps should apply at the normalized resolution, so we do not apply a timestep scaling. We see that the closest competitor to *Cardioid* is that of Niederer, whose time-to-solution is 500 times longer, and that the Krause effort is 3 times slower still.

VI. SCIENTIFIC CAPABLITY AND RESULTS

A. Anatomical reconstruction

We reconstruct anatomical models of the human ventricles from cryosectional images (see Figure 5) from the Visible Human Project® [6] of The National Library of Medicine. The female dataset is used since the cryosectional images have higher spatial resolution (0.33x0.33x0.33 mm) than those of the corresponding male dataset. A full description of this procedure is beyond the scope of this article. Briefly, the 2D images are segmented at organ boundaries and stacked to form a 3D structure from which is defined a 3D finite element mesh. We apply an additional transformation to define the Cartesian rectangular grid that is used in the code. To compute the conductivity for the diffusion calculation, we develop novel methods to define fibers, even within the smallest structures that were not resolvable with previous methods. For example, the complex surface geometry on the endocardium (inner layer of the ventricles; see Figure 1) was not accounted for in previous models of human hearts. Our resulting grids contain 370M (0.1 mm), 180M (0.13 mm), 89M (0.16 mm), and 44M grid cells (0.2 mm).

B. Impact of extension of reaction model

Sample results for the original and revised TT06 models are shown in Figure 6. The three cell types—epi, endo and M—have similar action potential duration (APD), the width of the spike in cell membrane potential after triggering (panel A). However, M cells do not show an accentuated prolongation with increased basic cycle length (BCL), the time interval between regular stimulus pacing. This deficiency is noted in the original papers and attributed to lack of a late sodium current in those models. With our addition of such a current, which is preferentially larger in M than in epi or endo cells

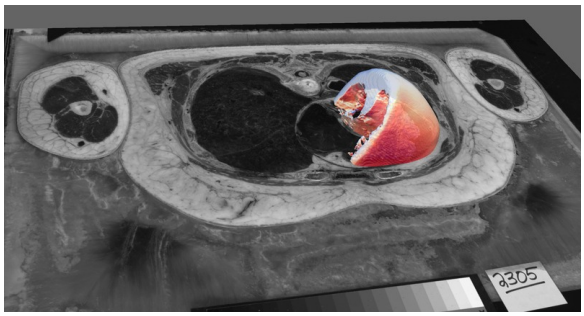

Fig. 5. Anatomical reconstruction of the 3D heart mesh from 2D images of the Visible Human Project.

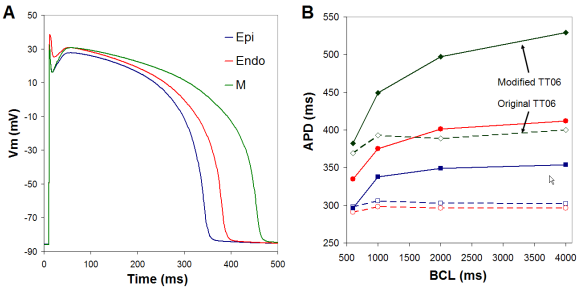

Fig. 6. Electrophysiological response in epi, M and endo cells. (A): AP's are shown for different cell types, labeled according to color, for 1000 ms basic cycle length (BCL). (B): The action potential duration at 90% polarization (APD90) is shown as a function of pacing rate for epi, endo and M cells for the original (dashed) and modified (solid) TT06 models. The modified model shows greater rate dependence of APD90, especially for M cells.

as characterized by experimental studies [17], [18], we are able to demonstrate a more realistic dependence of APD on basic cycle length (panel B). We also observe that in the original TT06, the endo and epi cells have roughly equivalent APD's, as suggested by early characterization in excised human slices [19], whereas in the revised TT06, the endo cells are intermediate between M and epi in accordance with more recent characterizations using higher resolution mapping [20] (panel B).

C. Wedge simulations

Torsade de Pointe (TdP) is an important class of arrhythmias that manifest as rapid undulations in the ECG with an envelope function that varies more slowly over time. The proposed mechanism of TdP [21], [22] involves heterogeneity of APD's and re-entrant activations in the ventricular wall. Canine wedge experiments suggest that the drug d-sotalol and slow pacing rates promote re-entrant activation around M cell islands [23]. Mirroring this, we simulate a human wedge (32x35x32 mm, 0.1 mm spacing) with M cell islands occupying roughly 30% of the volume of the wall [19] and located more toward the endocardium [20]. The action of d-sotalol is simulated by reducing the I_{Kr} current to 0. Like the experimental protocol in Akar, et al. [23], the wedge is brought to steady state with a regular train of stimulus pulses (termed S1) followed by an extra stimulus (termed S2), applied after a shorter interval, that can potentially trigger a re-entrant activation.

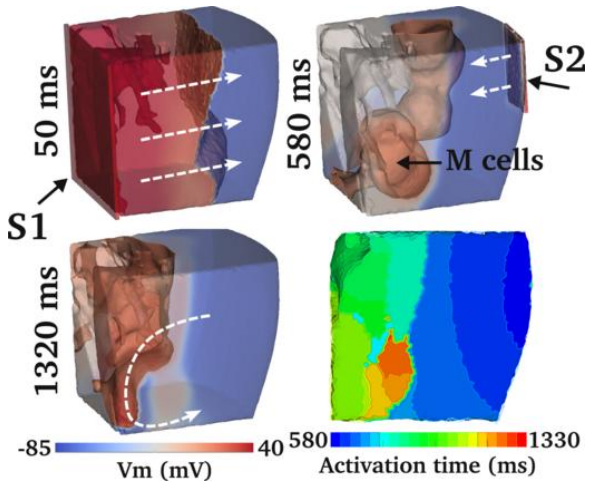

Fig. 7. Activation pattern in a wedge model with drug. The color shows the membrane potential as indicated by the scale bar (left). The last pacing stimulus (S1) is applied at 0 ms at the location of the red block and creates an activation wavefront (moving in the direction of the arrows) that has traversed roughly two-thirds of the wedge at 50 ms. A second stimulus (S2) is applied at 580 ms at the location shown by the smaller red block and produces a second activation wavefront. A re-entrant activation results as the wavefront travels around a functional block created by the M cells (see the arrow direction at 1320 ms). The lower right panel shows the isochrones of the wavefront with activation times indicated by the color bar (right).

Representative simulation results are shown in Figure 7. The last S1 stimulus is applied on the endocardial surface (left side) at 0 ms. The activation wavefront propagates in the normal direction from the endocardium to the epicardium. As in the experimental case, an S2 stimulus is applied on the epicardial surface to produce another wavefront of activation. The second wavefront begins to propagate in the opposite direction. The wavefront progresses in the direction of the arrows but the lower region cannot enter the functional block created by the M cells that is still depolarized and hence cannot be immediately excited again. The wavefront begins to wrap around the M-cell islands and eventually starts to cycle. The full trajectory of the wavefront can be seen in the isochrones. The activation wavefront can continue to cycle and can generate the rapidly undulating ECG in the wedge that is proposed to be analogous to TdP as measured in patients [23].

In the case with no drugs (not shown), the M cell islands and functional block are smaller, so that no re-entrant pattern is elicited for any S2 interval tested. The results correspond well with experimental data that re-entrant patterns are reliably triggered with d-sotalol and slow pacing, whereas few re-entrant patterns are elicited without such manipulations.

D. Whole ventricle simulations

While wedge results are promising, the power of our approach is best illustrated simulating the two ventricles and computing whole-body ECG's. Figure 8 shows results for the two ventricle model (0.10 mm resolution, 370M tissue grid cells) with the same scale bar as in Figure 7. Electrical stimuli are applied at points near the endocardial surface to simulate typical activation. At 20 ms, the activation wavefront is still

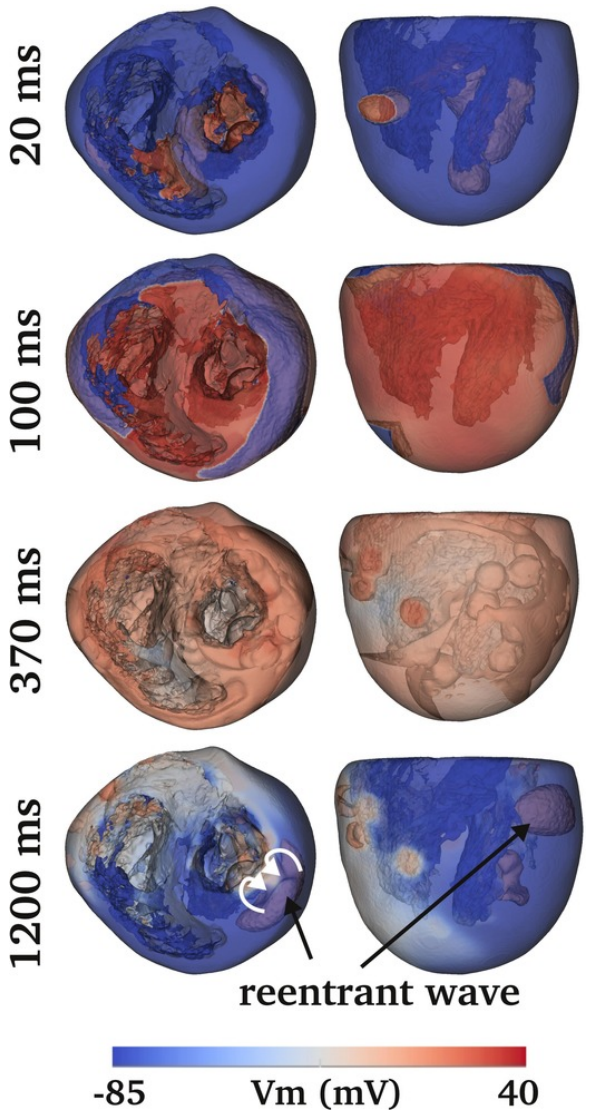

Fig. 8. Activation and relaxation pattern in the full two ventricle model with the drug application. The left column is a top-down surface view, and the right column is a cutaway with transparency to show activation fronts. The color codes the cellular potential with the same scale bar as in Figure 7. The front of electrical activation starts at the endocardium (20 ms) and propagates towards the epicardium (100 ms). During repolarization of the ventricles (370 ms), spherically shaped M cell islands are clearly seen, as M cells repolarize later than the surrounding tissue. An extra stimulus produces a re-entrant pattern (shown by arrows at 1200 ms) similar to the wedge case.

localized to the region near the initial stimuli. At 100 ms, the activation wavefront reaches the outer edge of the epicardial surface throughout most of the ventricles, while only the base (top of heart) and the apex (bottom of heart) remain in a relaxed state (indicated by the small blue regions), similar to experimentally derived maps in the seminal work of [24]. The activation eventually spreads to the whole heart (370 ms); repolarization then occurs as the heart cells return to the resting potential. As with the wedge, the M cell islands are visible, as these areas remain depolarized longer than the surrounding tissue. An extra stimulus on the epicardium produces a second wavefront that wraps around the M cell islands and begins to

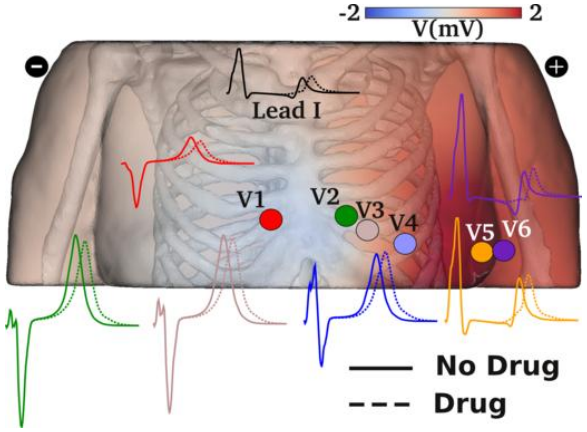

Fig. 9. Simulated ECG reconstructed from model of the torso. Using methods similar to those used for the heart, the torso reconstruction includes bones, fat and organs (lungs, spleen, etc.) that have different conductivities. The body surface potentials are then computed using the static diffusion equations with the heart as the source. Simulated ECG time traces are shown for Limb Lead I and precordial electrodes V1-V6 for cases with and without the drug. The complete body surface potentials are shown at the time of peak voltage of Lead I, with values according to the scale bar at the top of the figure.

cycle continuously in the directions indicated by the arrows at 1200 ms. While the pattern is more complex than that of Figure 7, the underlying mechanisms are essentially the same.

As an important validation, the ECG is simulated using a torso model as shown in Figure 9. Simulated ECG's show Limb Lead I traces similar to those clinically measured and also show typical morphological differences between precordial electrode positions V1-V6, as seen in actual patients. Moreover, the drug causes the T wave, the last positive deflection in the ECG, to be delayed, similar to clinical records collected several hours after administration of sotalol [7]. In the current simulation, the drug is assumed to have a maximal effect, but future work will involve simulations over hours, as administered drugs are slowly absorbed and cleared.

VII. Conclusions

We have developed a highly efficient and scalable simulation capability for human ventricular electrophysiology with groundbreaking detail and resolution to provide new insights into arrhythmia initiation and maintenance. The code solves a reaction-diffusion equation for the cell membrane potential using a standard ionic model of the human cell with novel modifications to better represent heterogeneous electrical properties of different cell types. We use an anatomical representation of the ventricles that, at 0.1 mm resolution, is best in its class for organ-level studies of arrhythmogenesis.

The code is optimized for the Sequoia BG/Q machine at Lawrence Livermore National Laboratory. The optimization approach combines biology-aware and hardware-aware tuning and utilizes both distributed and shared memory parallelism. The 64 hardware threads on a node are allocated to the reaction, diffusion and communication phases to maximize utilization of the hardware. We have demonstrated near-perfect weak scaling for a block of tissue cells using a range of processors representing 1/96 to 1/2 of the full machine, as well as excellent strong scaling on a human heart. The optimized code is a factor of 50 faster than the unoptimized starting point. Despite operating in an aggressive strong scaling regime with limited computational work per core, our scaling studies predict performance of 8.6 PFlop/s (43% of peak), and absolute throughput of roughly 9 heartbeats per minute (less than 65 μs per time step), for a 0.1 mm resolution 370 million cell grid on the full Sequoia. The corresponding time-to-solution is 400–500 times faster compared to previous methods.

The results of the scientific studies illustrate the power of the modeling approach. Consistent with experiments, the model shows that long action potentials of the M cell islands, accentuated by slow heart rates and d-sotalol, produce regions of conduction block that facilitate the formation of re-entrant activation patterns. To our knowledge, our simulations are the first to show re-entrant patterns in both wedges and human hearts. The model and its efficient implementation greatly advance the state-of-the-art and already provide an unparalleled method for interpreting and predicting electrophysiological responses that span from wedges to ventricles and to near-cellular scale. For example, the mechanism of whole-body TdP can be traced back to cellular responses in the wedge. Moreover, our method has the potential to make practical new cardiac modeling applications such as drug safety testing, medical device design, and therapeutic planning for personalized medicine. For example, we plan to replicate drug study experiments in human subjects that require multiple hours of simulation, a task far beyond the previous capabilities in the field.

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